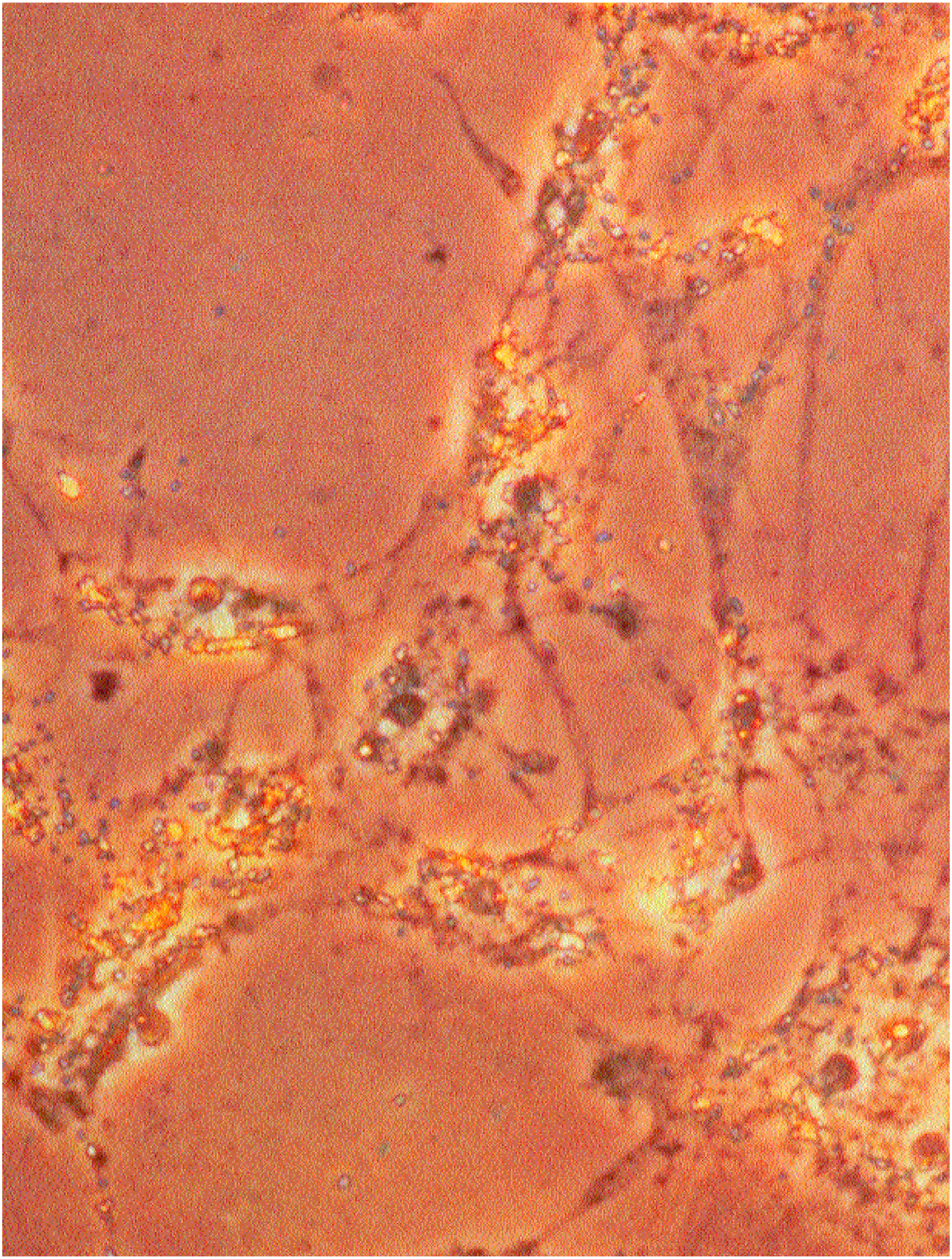

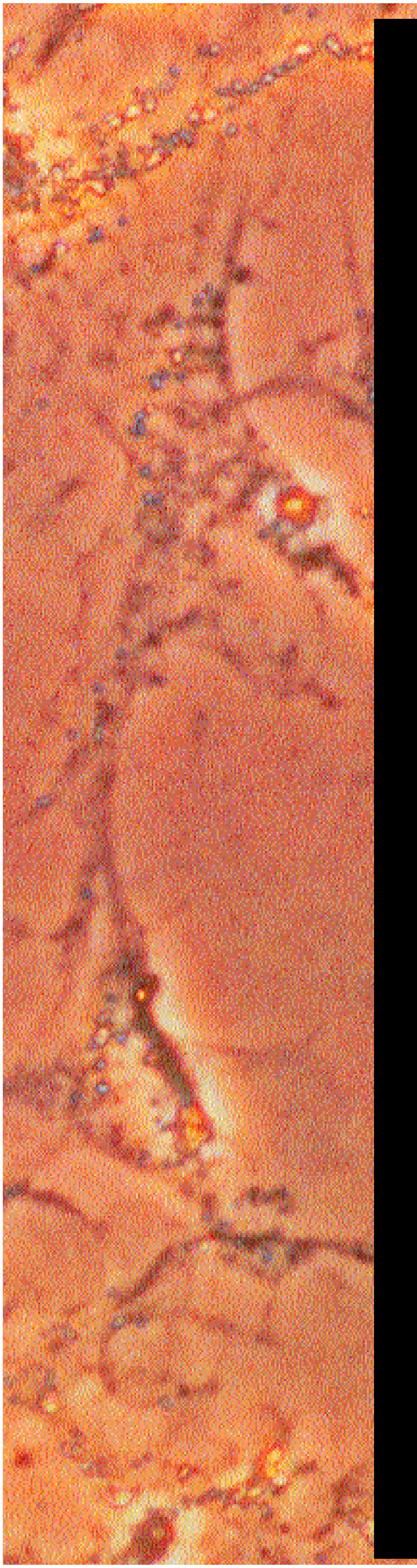

CHAPTER 3
INTERVENTION TECHNOLOGIES

When living systems fail because of disease or aging, medicine has at its disposal some truly amazing remedies. These nostrums range from outright replacement of the defective part, to modification of an existing one, to the general practice that most of us are familiar with. To effect these healing changes, a wide range of technology developments have been used. Microelectromechanical systems engineering, ion beam implanting techniques, new biocompatible materials, ultrashort electrical pulses, and lasers all play a part in these medical advances.

THIS CHAPTER INCLUDES THE FOLLOWING SECTIONS AND THEIR STORIES:

S E C T I 0 N   A
I M P L A N T S

Hearts can be replaced, but only with a donation from another human being. Luckily, less vital parts can be strengthened or supplanted by artificial components designed to produce minimal reaction from the host. The exception in the following series of stories is a miniature inertial unit that may be worn on the outside of the body, but the remainder are variations on the theme of better materials for biocompatibility, based on modifying the surface and structural characteristics of the implantable object.

1. A vest fitted with sensors that can provide tactile feedback signals to persons with balance disorders.

2. Stronger material components for hip replacement surgery.

3. Lightweight orthotics for knee and leg braces.

4. An ion-beam method for increasing battery lifetimes for pacemakers, meaning fewer surgeries.

5. Inserts to stabilize the spine to ameliorate the pain of trauma or degenerative disease.

MEMS SENSOR FOR BALANCE DISORDERS

● *The lightweight MEMS sensor may someday act as a cue to patients with inner-ear disorders.*

BMDO HISTORY

The Charles Stark Draper Laboratories (Cambridge, MA) developed a micromachining process for the manufacture of miniature inertial sensors using microelectromechanical systems (MEMS). The low-cost sensors combined the functions of a gyroscope and an accelerometer with an information processor to provide inertial guidance components for BMDO's Lightweight Exoatmospheric Advanced Projectiles program. The lightweight sensors have numerous applications in military and commercial technology, including precision-guided munitions, autopilot controls, airbag deployment, and medical electronics. In this last category, the micromachining innovation may lead to a unique way to help patients with balance disorders.

Vestibular disease can be detected by observing rhythmic movements of the eyes while instilling warm or cool water into the ears. In a normal subject, cool water causes the eyes to move in the opposite direction of the irrigated ear, and warm water causes movement toward it. The clinician can judge certain aspects of disease by watching how fast or how slowly the eye movements occur and whether movement is suppressed in a particular direction.

HOW IT WORKS

Draper Labs' micromachining process uses controlled chemical etching that can place up to 10,000 devices on a single silicon chip. The chips can be mass-produced, keeping production costs to a minimum. In addition, the low power requirements, small size, and complexity of the chip make it a versatile component for a lightweight feedback system. The chip's features have lent themselves well to a collaborative project involving the restoration of balance cues to patients with inner-ear disturbances.

MEDICAL SIGNIFICANCE

Vestibular (inner-ear) disorder is an uncommon but sometimes very debilitating condition that can be caused by transient viral infections, tumors, or trauma to the vestibular organs and nerves. Signals about the body's orientation in space (particularly rotational changes) are processed by a system of hair cells that are moved about by fluid flow within the inner ear's semicircular canals. These signals are relayed by the vestibular nerves to the brain, which in turn signals the body to make postural adjustments to maintain balance. Damage to the vestibular system can cause some patients to lose their sense of balance, resulting in recurrent dizziness that can greatly inhibit lifestyle and cause injury. In February 1997, researchers at Draper Labs, the Massachusetts Eye and Ear Infirmary (MEEI), and the Massachusetts Institute of Technology (MIT), with the support of the W. M. Keck Foundation of Los Angeles, began to consider the MEMS chip as a component in a feedback loop system that alerts patients when they begin to lose their balance. An initial system design would incorporate MEMS devices into a vest that can be comfortably worn by a patient. When one of the MEMS chips senses a deviation of a few degrees from vertical (indicating that the wearer is falling), a vibration is induced that alerts the wearer to correct the situation. An arrangement of chips can take the place of normal cues provided by the ailing vestibular system. Eventually, researchers hope that such an inertial guidance device could be inserted in the inner ear itself, much as cochlear implants are implanted in deaf patients.

VENTURES OR PRODUCT AVAILABILITY

This nascent work is part of the Balance Project in the W. M. Keck Neural Prosthesis Research Center at Massachusetts General Hospital. The center includes investigators from MIT, MEEI, and Draper Labs. The center's director is Donald Eddington, Ph.D., of the Cochlear Implant Research Laboratory at MEEI. Draper Labs is contributing internal funding to this project as well.

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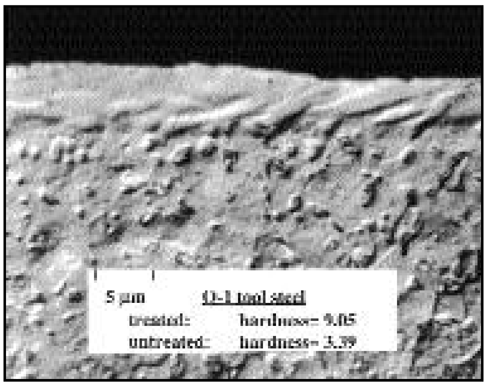
ION-BEAM SURFACE TREATMENT FOR IMPLANTS



● *IBEST can help strengthen the surfaces of weight-bearing artificial joints.*

BMDO HISTORY

Sandia National Laboratories (Albuquerque, NM) developed an ion-beam treatment technique called IBEST™ (ion-beam surface treatment) to modify surfaces of metals, ceramics, and plastic to make them more durable. The repetitive high-energy pulsed-power (RHEPP) accelerator developed for this treatment was funded in part by BMDO's Free Electron Laser weapons program and the Department of Energy's Inertial Confinement Fusion program. IBEST does not produce environmentally harmful waste products or residue, unlike predecessor technologies such as electroplating and other chemical processes. To commercialize the patented IBEST technology, two Sandia scientists obtained exclusive worldwide rights to IBEST and formed a new company called QM Technologies, Inc. (Albuquerque, NM).

More than 90 percent of hip replacements last at least 10 years. This statistic is expected to improve as materials and techniques evolve further.

HOW IT WORKS

RHEPP accelerators deliver short-duration, high-intensity ion beams. This combination of rapid pulsing and high energy allows controlled melting and surface modification of various materials. The heart of the RHEPP accelerator is a magnetically confined anode plasma (MAP) diode, invented at Cornell University. Through this device, an electrical pulse is delivered to a pre-ionized gas inside the MAP diode. The electrical pulse kicks ions out of the plasma that then travel through a vacuum to the surface to be modified. The IBEST ion beam can cover several hundred square centimeters at once. Very thin surface layers (2 to 20 micrometers thick) are rapidly melted and cooled, forming nanocrystalline grain layers without changing the atomic composition of the treated surface.

MEDICAL SIGNIFICANCE

Medical implants, especially weight-bearing hip joints for replacement surgeries, need to be durable. The longer a joint remains functional, the longer the patient can avoid a second surgery to replace a failed or worn implant. Modern artificial hips are often made of composite material, usually a ceramic that is coated with a durable metal, such as titanium, at the femur head (the "ball" of the ball-and-socket hip arrangement). Minute cracks in the metal coating allow calcium ions from the synovial fluid (lubricating fluid in the joint) to migrate through to the composite material of the replacement, causing the material to break down. IBEST treatment can minimize or eliminate these cracks, resulting in a longer-lived joint.

VENTURES OR PRODUCT AVAILABILITY

QM Technologies is currently evaluating materials used by companies manufacturing artificial joints with an eye to improving knee and hip joints with IBEST technology. IBEST also has many applications in the nonmedical arena, with development projects in the automotive, aerospace, and tool-and-die industries.

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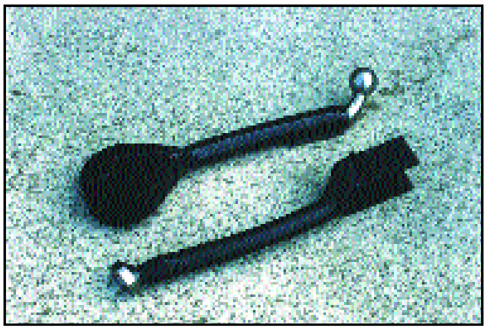
ADVANCED MATERIAL FOR ORTHOTICS AND IMPLANTS

BMDO HISTORY

SPARTA, Inc. (San Diego, CA), has developed composite materials for stronger, lighter-weight orthotics and medical implants. BMDO funded SPARTA's work in structural materials. The requirements for high stiffness and strength in a ground-based missile interceptor led to a composite material of graphite fiber and resin.



SPARTA's technology has been instrumental in improving hip, knee, and ankle joints.

Approximately 43 million Americans are regarded as having some sort of physical disability. New materials and both functional and anatomical modeling based on magnetic resonance imaging and computed tomography have brought much relief to such individuals.

HOW IT WORKS

SPARTA begins designing each orthotic or implant by selecting appropriate composite thermoset and thermoplastic compounds for the application, including those that are formable at low temperatures, lightweight, and low cost. Then it selects the length of the fibers. SPARTA's technology combines the best of continuous and chopped fibers, which provides the necessary formability yet retains the high strength of the materials. These materials can also be constructed for stiffness without malleability when needed, as in the ankle joints, knee joints, and foot plates.

MEDICAL SIGNIFICANCE

SPARTA's technology is especially useful when strong, lightweight materials are needed for full-leg braces, ankle joints, knee joints, foot plates, hip implants, bone implants, and spinal implants. External bracing is designed primarily for patients who have lower-extremity paralysis after spinal cord injury, with some limited applications for post-polio syndrome and congenital disorders. Composite orthopedic implants for repairing long-bone fractures and stabilizing spines are also under study.

The medical community's interest encouraged SPARTA to develop implantable biomimetic components, including femur and spinal implants. SPARTA—with the National Science Foundation; the University of California at Davis; Mekanika, Inc. (Miami, FL); the University of Miami, Department of Orthopedics; and Brent Adamson, M.D., (Kearney, NE)—studied repairing long-bone fractures with composite devices. The study used a composite femur implant for testing because of the strength required and the large amount of readily available data on steel implants. The information, methods, and synthetic materials used in the composite femur implant are also applicable to other long bones.

SPARTA, in a joint venture with Mekanika, is developing a spinal implant to immobilize vertebrae and has worked with the Defense Advanced Research Projects Agency to generate Food and Drug Administration data and commercialize the spinal implant. Mechanical testing is continuing along with cadaver studies. SPARTA is now working on testing the complete system, rather than the individual components, and is directing its energies to lowering the system cost.

VENTURES OR PRODUCT AVAILABILITY

SPARTA has worked with the National Rehabilitation Hospital (NRH; Washington, DC), the General Reinsurance Corporation, and Becker Orthopedic Appliance Company (Troy, MI) to develop lightweight knee and ankle joints. In particular, this effort resulted in an articulating drop-lock knee joint that can be either locked in the upright position for walking or unlocked for sitting, allowing the leg to bend. Both joints passed mechanical static and fatigue testing. The knee joint is in clinical trials, and the ankle joint is now in clinical evaluation at NRH. SPARTA has met its goal of reducing materials costs for the ankle joint.

The National Institutes of Health (NIH) is in discussion with SPARTA and the inventors of the “Seattle foot” for a prosthetic study. The Seattle foot is notable for its appearance in television advertisements in which double amputees play basketball. Currently, this venture is on hold because of SPARTA’s transformation from small business to large, which makes it ineligible for NIH Phase II SBIR funding. Proof of concept was successfully demonstrated under a Phase I SBIR contract.

SPARTA’s program manager for bioengineering of advanced material products is Moreno White, whose awards for bioengineering include the 1989 SDIO/ADPA Technology Transfer Award, the 1993 DuPont/ASM Composite Systems Award for the composite leg brace, and the 1996 Composites Institute's Award of Excellence.

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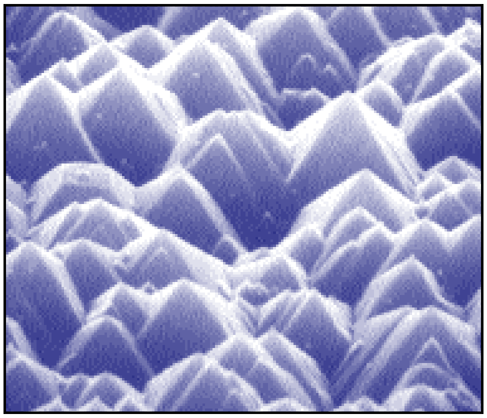
SPIRE'S ION-BEAM APPLICATIONS



● *SPI-TEXT creates random patterns on surfaces that can be useful for many biomaterials.*

Bacterial endocarditis is an infrequent complication of valve replacement surgery, but once acquired it can be fatal to nearly 60 percent of patients. It can also be acquired by rheumatic heart patients after simple surgery or dental procedures. In both cases it can usually be prevented with antibiotics.

BMDO HISTORY

With the help of BMDO SBIR contracts, Spire Corporation (Bedford, MA) developed an ion-beam texturization method that can create intricate surfaces on a variety of materials. For BMDO's Advanced Optical Baffles program, Spire used its patented SPI-TEXT method to create random patterns on optical sensors that aid in rejecting stray light. These sensors were used in BMDO's moon-orbiting spacecraft, Clementine, as part of the light collection system for star tracking. The same texturization method plays an integral role in Spire's biomaterial product line.

HOW IT WORKS

Spire developed an advanced surface modification technology based on ion-beam implantation and ion-beam-assisted deposition techniques. To produce optically dark surfaces, metals are bombarded with ions to create micrometer-scale textures, increasing surface area and providing light-trapping pores. For biomaterials that are either polymeric or metallic, this etching can alter surfaces for all manner of applications—for example, providing better anchoring for bacteria in petri dishes or, conversely, by coating and smoothing a catheter surface to prevent bacterial adherence.

MEDICAL SIGNIFICANCE

While medical procedures certainly save lives and alleviate suffering, many of the physical invasions associated with modern practices automatically introduce new problems. Any device that is inserted into the body carries with it a threat of infection. Bacteria are often particularly attracted to polymers in portions of hip and knee implants, as well as indwelling catheters and heart valve sewing cuffs. They easily take up residence on these devices in a resistant covering called a biofilm. Even bacteria that are normally eradicable by antibiotics can avoid harm by colonizing implants in this manner. In addition, rough surfaces on medical devices can promote the formation of clots that can travel to the lung, heart, and brain, with devastating consequences.

One of Spire's latest efforts has been in impregnating replacement heart valve sewing cuffs with silver metal through an ion-beam process called SPI-ARGENT. This coating of elemental metal helps prevent bacterial growth on the cuff, thus lowering the incidence of postreplacement endocarditis, a life-threatening infection of the heart's inner lining. In early June 1997, Spire announced an exclusive agreement with St. Jude Medical, Inc., to develop the heart-valve sewing cuff. St. Jude produces mechanical heart valves that are considered the gold standard in the industry. Using related technology, Spire also treats central venous catheters and surgical guide wires to reduce the likelihood of clot formation and increase lubricity, which eases the insertion process.

VENTURES OR PRODUCT AVAILABILITY

Spire's registered and trademarked techniques include the following:

IONGUARD enhances the mechanical and chemical surface properties of titanium alloy, cobalt-chromium, and other metal and ceramic orthopedic or dental devices. Overall, this process makes artificial joints more durable by increasing wettability and reducing friction; it also enhances adhesion to biocompatible cements.

SPI-TEXT texturizes electrodes used in cardiac pacemaker batteries. The increased surface area improves tissue attachment and decreases electrical resistance at the contacts. Testing showed that battery lifetimes were increased by 300 percent, electrode resistance was reduced, and battery weight was decreased. SPI-TEXT was licensed by a cardiac pacemaker manufacturer in 1993.

SPI-ARGENT treats polymer, metal, and ceramic medical devices to reduce the material's ability to induce blood clotting (increase thromboresistance), to reduce bacterial adhesion, and to improve hardness, slickness, and bondability of surfaces.

Spire's recently introduced line of central venous catheters is treated with a process called SPI-POLYMER. The process is designed to create a slick and thromboresistant surface for catheters.

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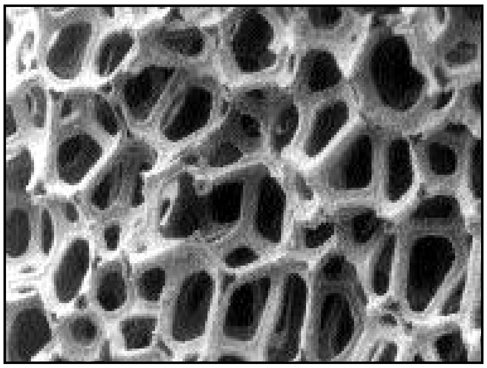
NOVEL MATERIAL FOR SPINAL IMPLANTS

BMDO HISTORY

Ultramet (Pacoima, CA) received SBIR funding from BMDO to develop insulator materials for rocket nozzles. From this research, the company successfully manufactured synthetic cellular foams that can serve both as insulators and as kinetic energy absorbers. The foams are made of ceramic, metal, and glass and can be used for biomedical, environmental, and construction applications.

In evolutionary terms, the human spine is an imperfect support system because of our fairly recent adaptation to the upright position. It was really designed for creatures who move on all fours. Back pain and spinal disorders are prevalent in human lives, largely because of this engineering glitch.



● *Ultramet's synthetic cellular materials are readily compatible with natural bone.*

HOW IT WORKS

Ultramet's materials are composed of a carbon foam skeleton that is treated by a chemical vapor deposition (CVD) method to lay down a coating of various compounds and elements. Through CVD, a continuous thin film of metals such as rhenium or tantalum, or compounds such as silicon carbide, can be distributed throughout the interior of the construct, lending certain thermal or tensile properties to the carbon foam substrate and to the structure as a whole. The resulting products are characterized by low cost, low density, high chemical purity, controlled thermal expansion, and high thermal stability. Depending on the coating used, the material can be made resistant to oxidation and can withstand temperatures of up to 6,000° F. The high strength and porous structure of one Ultramet product, Hedrocel®, makes it especially useful as a biocompatible replacement for the vertebral bodies that make up the spinal column. Hedrocel is a tantalum-coated carbon porous matrix product that mimics the properties of, and is compatible with, bone.

MEDICAL SIGNIFICANCE

The problems of the aging spine can be traced, at times, to loss of soft tissue between the vertebrae. This can lead to pain from compressed spinal nerves. Cancer that has metastasized to the spine, degenerative diseases such as arthritis, and trauma can also compromise soft tissue. Hedrocel was licensed by Implex Corporation (Allendale, NJ) to be used in replacement discs for the spinal column. Specifically, the replacement acts as a spacer in support of the vertebral body, or the round portion of the disc. The porous natural structure of bone is simulated by Hedrocel, and bone can gradually infiltrate into the artificial disc just as it would into a damaged section of natural bone. The vertebral body implant is screwed into place, sometimes with a cement accompaniment, and consolidation takes place as the bone and Hedrocel implant fuse together. The fusion obviates the necessity for the soft tissue disc, and the two bony processes grow together, reducing the possibility of nerve compression and therefore pain.

VENTURES OR PRODUCT AVAILABILITY

Early animal studies funded by the National Institutes of Health spurred Implex to build facilities specifically for Hedrocel implant products. Hedrocel vertebral implants were then used in eight European patients in late 1994. They are currently being used in a United Kingdom trial of 25 patients, specifically for replacement of the lower cervical vertebrae. Implex is also planning to manufacture devices for the small joints of the fingers, as well as components for hip replacements.

Ultramet owns the patent on the carbon foam process. Ultramet licensed the technology to Implex, which trademarked Hedrocel.

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SECTION B
TREATMENT

Lasers have found their way into medicine, replacing scalpels in some cases, augmenting drug-tissue interactions, reducing discomfort in dental procedures, and reshaping the surface of the eye. Based on funding from BMDO's Medical Free Electron Laser (MFEL) program in the mid-1980s through the early 1990s, photomedicine became a true specialty. In 1996, the first photodynamic therapy drug, Photofrin, was approved for the treatment of esophageal cancer. This drug, its cognates, and second-generation derivatives were studied in depth at a number of clinical centers and universities, thanks in large part to the MFEL program. Also represented here is a sterilization method for liquid and solid foods, a timely subject in light of the recent rash of food- and water-borne illness in the United States.

1. Two world-recognized facilities that perform state-of-the-art photomedical research and provide clinical treatments for skin disorders and cancer and develop laser-based imaging technologies.

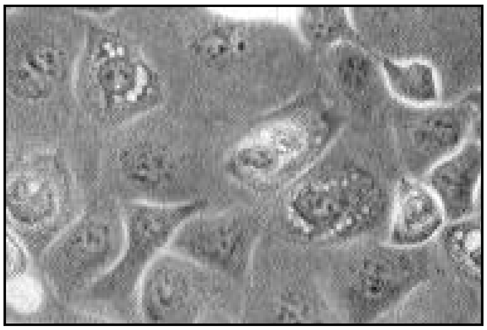
2. New collagen-bonding treatments for joint disorders and improved outcomes for lens replacement surgery.

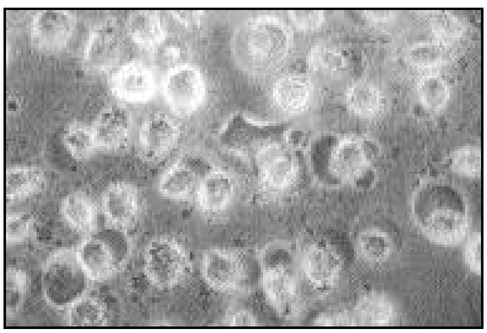
3. A "cool" sterilization technology that kills deadly ***Cryptosporidium*** and leaves foods and liquids unaltered.

4. New laser therapy for effective cavity prevention and practically painless root canal treatment.

5. Ultrafast switches for lasers, electroporation devices, and a novel tomographic imaging technique.

WELLMAN LABORATORIES OF PHOTOMEDICINE





Photodynamic therapy can selectively destroy cancerous cells.

BMDO HISTORY

During the late 1980s, BMDO funded the MFEL program to allow medicine to leverage the Defense Department's advanced laser technology. With help from this initiative, Massachusetts General Hospital (Boston, MA) nurtured a combined research and clinical laboratory that came to be known as the Wellman Laboratories of Photomedicine. In this brief period, Wellman has achieved worldwide recognition for its excellence in light-based medicine, as well as a pioneering milestone in cancer treatment called photodynamic therapy. Thus, technology transfer from the high-powered free electron laser, originally conceived to kill enemy missiles, has enabled destruction of a different sort.

Lasers have revolutionized the lucrative practice of cosmetic surgery and related services. For depilation alone, where lasers have just made an entry, the U.S. market is estimated at $1 billion.

HOW IT WORKS

The discrete wavelengths and short, well-controlled pulses of laser devices allow clinicians to investigate and observe specific physical interactions. For instance, certain skin pigments such as melanin absorb light at a particular wavelength, as does the hemoglobin in red blood cells. Researchers can take advantage of these particular traits and tailor new therapies to old disorders. The MFEL program allowed researchers access to powerful free electron lasers, which in turn led to insights for new applications of Nd:YAG, carbon dioxide, and other medically useful lasers.

MEDICAL SIGNIFICANCE

Photodynamic Therapy. Wellman Laboratories of Photomedicine has developed a wide range of light-based therapies. The most notable among these is photodynamic therapy (PDT), a method of killing tumors and other diseased tissues that has been approved by the Food and Drug Administration (FDA). Lasers are a critical part of PDT because a precise wavelength of light is needed to activate the tumoricidal drug. In this case, the drug is Photofrin, a compound that is preferentially absorbed by cancer cells. The drug remains inactive until exposed to light, whereupon it releases high-energy oxidation products that kill the tumor, in a manner similar to how the immune system eliminates damaged or diseased cells. Normal tissue is spared, and there are few undesirable side effects. Second-generation photoactive drugs such as benzoporphyrin derivative are also being tested for efficacy in PDT, and the applications are not limited to cancer. Rheumatoid arthritis, psoriasis, endometriosis, macular degeneration, and regrowth of arterial plaque after angioplasty are all conditions that are being treated experimentally with PDT.

Laser Treatment of Skin Lesions. Before lasers were accepted as a clinical tool, pigmented skin lesions such as the purplish-red port-wine stain and the common hemangioma, or "strawberry mark," were not satisfactorily treatable. Lesions that appear on the face are cosmetically disturbing to the patient, and occasionally a hemangioma can threaten eyesight or obstruct the nose or mouth. Researchers at Wellman have achieved truly remarkable results with laser treatment of these lesions. Copper vapor lasers and Nd:YAG lasers are used to deliver a 585-nanometer laser beam to the affected area. After repeated treatments, the red pigment (from hemoglobin mostly) fades away, and the normal color of the skin emerges.

In a related therapy, superficial capillaries, or spider veins, can also be treated with lasers. Wellman uses a 595-nanometer laser to obliterate these unsightly but usually harmless veins. The alternative treatment, called sclerotherapy, involves injection of saline solution or other sclerosing compound that collapses the blood vessel walls. Sclerotherapy can be painful and can result in discoloration that is more objectionable than the original condition. For cosmetic concerns of another sort, Wellman is also developing a method of laser depilation, similar to a technique that is now on the market. The difference in Wellman's technique is that the laser is used without preapplication of a light-absorbing lotion. Thus far, studies have shown that the laser method can prevent hair regrowth for up to 31 weeks.

Laser-Induced Fluorescence of Cancerous Lesions. Laser-induced fluorescence spectroscopy has become an exciting window into the cell. Precise wavelengths induce precise excitations, and cancerous lesions can be seen as bright spots that can be well distinguished from their normal surroundings. In endoscopically accessible regions of the body, such as the bladder, esophagus, and lungs, a fiber-optic probe can deliver laser light and then transmit the fluorescence response to a spectrometer, which analyzes the returning light. At Wellman, doctors are using this technique to inspect the bladder wall in order to distinguish cancerous lesions from normal tissue. After comparing unique fluorescence patterns, a false-color imager can show the doctor a well-defined picture of the tumor, allowing successful excision and avoiding surgical damage to the nondiseased portion of the bladder.

VENTURES OR PRODUCT AVAILABILITY

Wellman continues to develop and implement novel treatments involving the use of light and photochemicals. Approximately $250 million in commercial revenues have been generated by the laboratory's photomedicine activities, mostly through sales of medical lasers.

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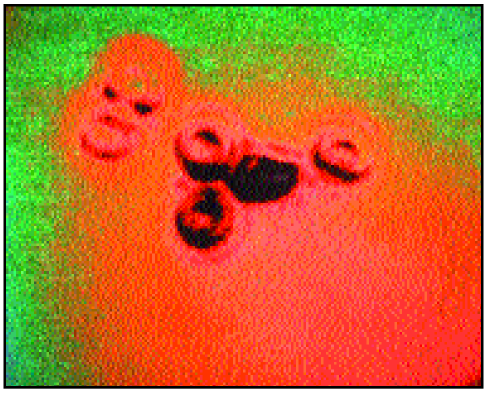
BECKMAN LASER INSTITUTE ADVANCES



Beckman's researchers use "laser tweezers" to isolate and examine single cells.

Recent in vitro studies suggest that low-level ultrasound can be used in place of light to activate PDT drugs. An advantage of this approach would be to eliminate invasive fiber-optic light delivery systems and laparoscopic access to internal structures.

BMDO HISTORY

Along with other centers of excellence such as Stanford and Baylor Research Institute, the Beckman Laser Institute (BLI; Irvine, CA) received funding through the MFEL program. Like the Wellman Laboratories of Photomedicine (Boston, MA), this institute has made many advances in photomedicine in areas such as photodynamic therapy (PDT) and laser treatment of dermatologic diseases. BLI was established in 1982 as an international center for laser studies and includes a medical clinic that functions as an outpatient facility of the Medical School of the University of California at Irvine. Other areas of interest include treatment of cataracts, glaucoma, and gynecological conditions, and novel imaging modalities.

HOW IT WORKS

Most living tissues exhibit some wavelength-dependent absorption, reflection, and transmission. By taking advantage of these discrete differences in laser-matter behavior, researchers can tailor laser-beam wavelengths to a particular target without harming surrounding tissue. The laser-matter interaction can be direct or can be assisted with drugs that are preferentially absorbed by a target tissue.

In addition to treating diseases, laser light energy can be used to create optical traps and to cut cellular components. "Laser tweezers" and "laser scissors" are now becoming a recognized part of the biological tool kit. Laser transmission, reflectance, and scatter through tissue can also be used to create both macroscopic and microscopic images and to collect data for spectral analysis.

MEDICAL SIGNIFICANCE

Photodynamic Therapy. PDT will very likely be adapted as a regular part of the cancer treatment pharmacopoeia in short order. For reasons not yet well understood, abnormal tissues collect the photosensitive drug preferentially, while normal tissues collect far less. When light of a specific wavelength is applied to the treated area, a toxic oxidative reaction takes place. The reaction kills tumor cells but spares normal tissue—a "surgical strike" without surgery. So far, PDT has shown itself to be generally nontoxic to healthy tissues when compared with conventional chemotherapy, which damages all tissue. PDT also seems not to encourage drug resistance, a problem that frequently occurs in repeated cancer treatments. A recently approved drug, Photofrin, is part of a newly FDA-approved PDT regimen (currently limited to end-stage esophageal cancer) and is just one of the drugs being tested at BLI. The institute's researchers are using a number of PDT protocols, along with second-generation PDT compounds, to treat cancers and gynecological disorders.

Novel Imaging Device. Bruce Tromberg, Ph.D., and a group of medical researchers at BLI have developed a fast, portable near-infrared spectrometer to probe for tissue abnormalities, such as breast tumors. The optical device uses a new optical imaging modality, called frequency-domain photon migration, which is safe, noninvasive, inexpensive, and potentially more sensitive and accurate than other imaging techniques.

To detect abnormal breast tissue, the handheld laser diode instrument sends near-infrared light through the tissue to determine its optical properties. As light propagates through tissue, the researchers measure how many photons were scattered or absorbed. These data can then be interpreted to yield tissue hemoglobin levels, blood volume, and water content. With this information, certain diagnoses can be made.

For example, a great deal of scattering might signal high cell density, a sign of cancer. Malignant tumors also may absorb more light because they contain more hemoglobin than normal tissue. Fluid-filled cysts should have lower than usual scattering, because the density of fluid is lower than that of normal tissue.

Laser Tweezers and Scissors. Beckman's director, Michael Berns, Ph.D., and Tromberg have collaborated to develop devices such as laser tweezers and scissors that can be used to immobilize and manipulate cells and their contents. Berns's early interest in chromosome cutting has led to the ability to optically cut lengths of DNA and selectively amplify these sequences. Currently, molecular biologists use a variety of wet chemistry techniques to enzymatically cut DNA (with restriction endonucleases derived from microbes). The laser scissors device, if cost-effective, is a cleaner, more direct alternative to endonuclease cutting; moreover, restriction endonucleases can be used at only a limited set of four- to eight-nucleotide sequences in the genome. The laser tweezer, scissors, and the free electron laser based microscope are basic research tools at present.

VENTURES OR PRODUCT AVAILABILITY

Photofrin, manufactured by QLT Photopharmaceuticals (Vancouver, BC) was approved for treating late-stage esophageal cancer in late 1996 and is being used in a number of clinical centers, including BLI, for PDT. PDT for noncancerous conditions such as endometrial hyperplasia is also being assessed, as well as novel photosensitive drugs.

Through a collaboration with the Chao Family Clinical Cancer Research Center (Orange, CA), Tromberg is testing the tissue spectrometer's ability to differentiate between normal and abnormal tissue. He and John Butler, M.D., have gathered and analyzed data on about 30 patients. The researchers are now correlating these data to such conventional techniques as mammography and histopathology.

Tromberg says that the results look promising at this point: the data correctly predicted a fluid-filled cyst in one patient and a fibrous tumor in another. He anticipates more extensive clinical trials within two years. Ultimately, he hopes the research will result in a needle-free breast cancer detection device to complement, not replace, mammography. Tromberg's team received a patent for frequency-domain photon migration in 1992.

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BAYLOR PHOTOSENSITIZING AGENTS

● *Baylor has a new drug that can help maintain vision clarity in lens replacement patients.*

Approximately 40,000 corneal transplants are performed every year on an outpatient basis under local anesthetic.

BMDO HISTORY

In the early to mid-1980s, BMDO supported the MFEL program, designed to transfer military expertise in laser development to the medical sector. Baylor Institute (Dallas, TX) was just one recipient of MFEL funding. Large, expensive free electron lasers were not (and indeed are still not) commonly available, and the biological benefits of the lasers' broad wavelength range were therefore hard to realize. The MFEL program offered medical scientists a chance to use the lasers' versatile characteristics, and attendant observations of tissue-wavelength interactions, to further develop their hypotheses. A very large number of clinically significant outcomes resulted from this collaboration. Among them were the development of photosensitive agents that can be used in treating cataracts and even cancers.

HOW IT WORKS

The wide wavelength range afforded by free electron lasers helped researchers explore a greater variety and more discrete assortment of laser energies and frequencies. Most materials, including biological tissues, absorb light markedly well at a certain wavelength, while handily reflecting light at others. Hemoglobin, for instance, absorbs very strongly at between 580 and 600 nanometers, corresponding to the green-yellow part of the spectrum. For this reason, laser therapy of hemoglobin-rich birthmarks such as port-wine stains has found resounding success in recent years. The hemoglobin, and not the surrounding healthy skin, absorbs the intense energy of the coherent light, and the unsightly red marks break down and fade. Similarly, other cellular components react in predictable ways when they absorb light, and through the activity of photochemicals, they can be targeted by light activation.

MEDICAL SIGNIFICANCE

The latest advances at Baylor include a photochemical method of removing tumor cells from bone marrow in preparation for autologous transplant. In patients who have a relapse following chemotherapy for cancer, a more vigorous and potentially toxic chemotherapy protocol is now used. To prevent irreparable damage to the marrow stem cells, the marrow is removed and stored while the patient undergoes therapy. Baylor researchers are studying the use of photochemicals and light on the marrow cells as a means of ensuring that the marrow will be purged of any residual tumor cells. Thus when the marrow is returned to the patient to reconstitute the blood and immune system, the danger of cancer recurrence is reduced. Other chemical methods of purifying marrow stem cells kill about 80 percent of the stem cells. The photochemical method preserves 80 percent of the stem cells. It is projected that a larger number of surviving stem cells will increase the likelihood of a successful take of the cells upon transplantation.

Researchers at Baylor have also developed a photochemical treatment for cataract patients. Cataracts, or proteinaceous growths on the lens of the eye, can obscure vision to the point of blindness. Lenses can be replaced with surgery, but 30 percent of patients experience exuberant regrowth of tissue over the lens as a result of an overactive healing process. A new surgical adjunct method uses naphthalimide dye and blue laser light to treat the capsule, or lens implant site, before placement of the new artificial lens. This intervention reduces tissue regrowth that can obscure the new lens.

A novel photoactive dye that inhibits the activity of collagenase and links adjacent collagen fibrils together is also under investigation. Collagen is a fibrous protein that serves as a connecting and supporting structure in connective tissues throughout the body. Collagen is the primary protein found in the tendons, ligaments, bone, cartilage, skin, organ capsules, and cornea and sclera (white) of the eye. During tissue remodeling and following trauma, collagenase, an enzyme that disrupts the bonds between collagen strands, is released to digest the collagen. The photochemical bonding is achieved by painting a photochemical on a damaged surface of a torn tissue, such as the cartilage meniscus in the knee joint or a torn surface of a cornea, and then exposing these surfaces to a blue laser light. This causes the formation of new bonds between adjacent collagen fibrils and also makes them resistant to further degradation by collagenase. This new approach to tissue bonding offers a sutureless system that is more efficient at healing the treated surface.

VENTURES OR PRODUCT AVAILABILITY

The ophthalmology applications are being investigated further in a joint effort between Baylor researchers and investigators at the Kansas Eye Institute. Additional studies on the toxicity and metabolism of the photochemicals are in progress to enable clinical testing of the stem cell procedure and collagen bonding procedure in humans. Work on the collagen linking was partly supported by the MFEL program and the Arthritis Foundation. Patents on the dye synthesis and applications are issued to the inventors.

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HIGH-ENERGY CAPACITORS TO HELP ZAP MICROBES

PurePulse has introduced a fast and effective method for eliminating deadly bacteria, viruses, and other microorganisms.

BMDO HISTORY

PurePulse Technologies, Inc., a subsidiary of Maxwell Technologies (San Diego, CA), has developed a highly efficient FDA-approved method for killing parasites, bacteria, and viruses in water, on the surfaces of medical and food packaging, and in liquid foods. Dubbed PureBright® and CoolPure®, the two systems deliver, respectively, microsecond bursts of intense light or a pulsed electric field to rupture the membranes of pathogenic microbes. Based on advanced high-energy capacitors, the systems offer kill rates 100 to 10,000 times those of conventional mercury lamp ultraviolet treatments. BMDO partially funded development of these capacitors to produce a compact, lightweight device that could provide pulsed power for space-based lasers and accelerators.

A major outbreak of waterborne *Cryptosporidium* occurred in the summer of 1993, sickening about 400,000 people in the Milwaukee area. There is no effective treatment for this parasite, which can also be spread through foods, juices, and personal contact. Water filtering and hand washing are good preventive measures.

HOW IT WORKS

Capacitors accumulate electrical charge and energy on the surfaces of conducting plates that are insulated from each other by a dielectric material. Maxwell developed its capacitors by using insulating materials with a higher dielectric constant, reducing the thickness of the insulating material, increasing the voltage between the conductors, and reducing the thickness of the conducting plates. Through this combination, Maxwell successfully produced its high-density thin-film capacitors, which have been used to power implantable cardiac fibrillators. PurePulse used this same technology to develop its purification systems.

MEDICAL SIGNIFICANCE

PureBright has been shown to kill the deadly *Cryptosporidium*, a recently resurgent pathogen in municipal water systems. Moreover, the organism is killed in the oocyst phase, a particularly resistant stage in its life cycle. Viruses are also eliminated by the system. PureBright is designed to treat clear fluids, but it also effectively kills bacteria, mold spores, and viruses in air ducts and on filter surfaces. Used with ultraviolet-transmissive polymers such as polypropylene or polyethylene, PureBright can also sterilize saline solutions in intravenous bags, making sterilization a one-step process. Other applications include sterilizing packaged foods, decontaminating cup and lid packaging, and treating fresh meats, fruits, and vegetables to prevent microbial degradation and eliminate contamination.

CoolPure preserves opaque liquids such as milk, soups, and juices without heating and therefore without denaturing the treated product. As most people are accustomed to the flavor of heat-pasteurized milk, they may find CoolPure-treated raw milk an acquired taste. However, retention of raw milk components such as rennin, the curdling enzyme, is important for cheese production. CoolPure is bactericidal at temperatures from 25°F to 60°F and is designed to treat pumped liquids as they are flowing. The quick treatment time ensures an acceptable product flow rate. CoolPure may also enhance the yields of some pharmaceutical and biotechnical processes.

VENTURES OR PRODUCT AVAILABILITY

PurePulse is in discussion with leading medical manufacturers for various sterilization applications. The company has contracted with a large international fast-food chain for decontaminating water, the U.S. Army for sterilizing food, and a manufacturer for treating liquid whole eggs. PurePulse configures its systems to the user's needs and welcomes inquiries.

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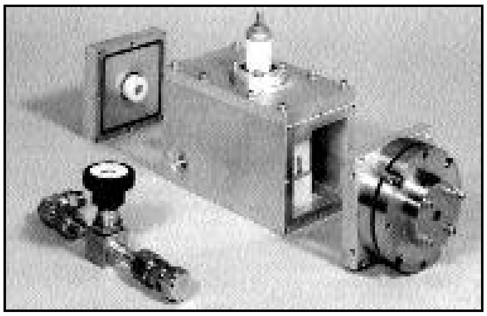
CARBON DIOXIDE LASERS FOR MEDICAL APPLICATIONS



● *QSource's air-cooled lasers are poised to enter the medical and dental markets.*

BMDO HISTORY

QSource, Inc. (East Hartford, CT), received both Phase I and II SBIR funding for building compact, lightweight carbon dioxide (CO_2) lasers for LADAR systems. In 1996, QSource won a Phase II contract through the new SBIR Fast Track program, with Medical Optics, Inc. (MOI; Carlsbad, CA), providing the matching funds.

Although a third of today's youngsters between 5 and 17 are cavity free, tooth decay remains second only to the common cold in disease prevalence.

HOW IT WORKS

QSource has licensed its radiofrequency, direct-current (RF-DC) CO_2 laser to MOI for medical and dental applications. Dental applications are one of the initial target markets for QSource's modular laser technology, which also has good industrial potential. In addition, these lasers are suitable for existent and emerging soft-tissue medical treatments, such as laser skin resurfacing.

QSource's sealed, air-cooled CO_2 laser is a modular, repetitively pulsed instrument that employs a sealed tube configuration and a hybrid RF-DC electrical discharge lasing mechanism. The design's advantages are system reliability, ease of maintenance, and device life over conventional CO_2 lasers. The design makes possible less costly manufacturing methods in production. It achieves high power output with its combined RF-DC excitation mode, which produces peak pulsed power levels (as high as 1 kilowatt) several orders of magnitude higher than the average output power. The sealed design also allows system flexibility and portability, since the laser need not be connected to an umbilical gas line. It can also operate in a continuous-wave mode and boasts a lifetime of more than 1,000 hours in the product configuration.

MEDICAL SIGNIFICANCE

CO_2 lasers are already in widespread use in the medical realm, and with the pulsed power capability of QSource's design, these lasers have promising dental applications. In MOI-sponsored research at the University of California at San Francisco Dental School, 9.3-micrometer-wavelength laser pulses are being investigated as a way to seal tooth enamel and inhibit dental caries (cavities). Studies suggest that rapid pulsing of teeth can make them five times more resistant to caries formation, and in some cases, the laser treatment can even remineralize areas of incipient decay. The brief treatment is less time-consuming than fluoride treatment (which can discolor teeth) and polymer sealant application.

Another significant research area is laser pulpotomy, or laser treatment of dental pulp, the vital portion of the tooth. At Beckman Laser Institute (Irvine, CA), MOI's CO_2 lasers (also designed with QSource technology) are being used in dogs to treat pulp infections. The laser method removes inflamed tissue before infection can destroy the whole tooth, and it leaves healthy tissue intact so that the tooth remains functional and retains its living root. The method may become an alternative to root canal therapy, a painful procedure that millions of human patients undergo each year. Unlike the forceful physical debridement methods of conventional root canal therapy, laser treatment is expected to result in better tooth retention and reduced future complications.

VENTURES OR PRODUCT AVAILABILITY

David Nielsen, D.V.M., a Manhattan Beach, CA, veterinarian, has been using the CO_2 laser in his canine dental practice since 1995. He works in collaboration with Petra Wilder-Smith, D.V.M., and George Peavy, D.V.M., of the Beckman Laser Institute. Documentation of this work will eventually be used to justify human trials.

MOI, a subsidiary of Kaiser Aerospace and Electronics, has agreed to provide matching funds for technology development in the Fast Track Phase II agreement, the total of which amounts to $1 million over two years. MOI sponsors research at the University of California at San Francisco in dental applications and plans to market QSource technology for the many procedures that the FDA has already approved for CO_2 lasers.

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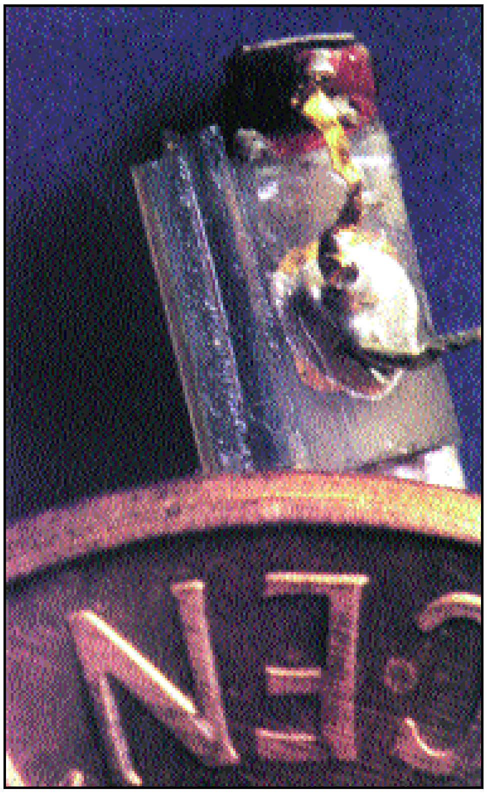
ULTRAFAST LIGHT-ACTIVATED SWITCHES

BMDO HISTORY

Energy Compression Research (ECR; San Diego, CA) has developed a revolutionary ultrafast semiconductor switching technology called light-activated silicon switching (LASS). With contracts from the early days of BMDO research, ECR focused its efforts on developing photoconductive switches that have applications in electronics, electro-optics, and photonics for weapons such as the electromagnetic gun.



● *The minuscule silicon switch has multiple applications in biotechnology and medical imaging.*

Electroporation is now a workhorse application for molecular biology, where it is used to transform bacteria, yeast, and human cells with foreign DNA, enabling *E. coli*, for instance, to secrete mammalian proteins like insulin or interferon.

HOW IT WORKS

ECR's LASS technology involves semiconductor devices that use laser light to switch a current on or off. Semiconductors are ubiquitous in the electronics industry, where they function as power amplifiers, storage modules, and switches. Switching current on and off is the most general function of the semiconductor. Conventional semiconductor switching time is governed by the speed at which electrons traverse the switch. The LASS device uses the absorption of laser light to create the conducting electrons within the semiconductor, resulting in a thousandfold increase in switching time compared with conventional switches. The high-speed, low-jitter, and zero-delay LASS device can be used to power lasers, route signals in fiber-optic communications devices, control industrial motors, and power high-frequency radar communications. LASS technology offers high efficiency and cost savings in these areas.

MEDICAL SIGNIFICANCE

ECR is currently developing LASS technology for applications in the medical industry. One area of concentration includes analytical instruments such as flow cytometers, mass spectrometers, and fluorescence lifetime spectrometers. Lasers designed by ECR provide high reliability as well as a compact footprint for these devices.

A second medical application is in imaging systems. ECR is looking to the far-future application of optical diffuse tomography, a technology that may enable doctors to perform mammography without ionizing radiation. This technology was envisioned more than a generation ago as "diaphanography," a method that is familiar to anyone who has shone a flashlight through his or her hand. For breast tissue, however, high-intensity visibleto-infrared light is necessary for penetration and visualization, and a means of optical gating must be used to reconstruct the image. Technologies such as LASS devices and better understanding of the optical properties of living tissue are stimulating interest in this field.

ECR lasers offer well-defined short pulses with high repetition rates for surgery, particularly eye surgery.

In electroporation, an intense short pulse of electricity is used to provide the force that opens cellular pores, enabling the insertion of macromolecules like DNA into cells of interest. It is a commonly used method for basic research in biology and for "transfecting" cells in genetic studies. However, many cells are sacrificed in the process; up to 50 percent are destroyed when using a DC power source to induce pore formation. LASS technology can reduce cell loss to 10 percent by using a square-wave pulse to effect rapid and reversible pore formation.

VENTURES OR PRODUCT AVAILABILITY

ECR manufactures microlasers, fast Pockels cell drivers, and laser diode drivers. The microlaser series is an established commercial product that is distributed worldwide. Microlasers are being used in temperature sensor systems, scientific instruments, and a broad range of product development areas, including biomedical, electrical utility, micromachining, and defense systems.

The Pockels cell driver is also a commercial product that uses ECR's LASS technology as the heart of the system. It is used in a variety of lasers and switches at megawatt power levels and picosecond speeds.

ECR also manufactures and distributes solid-state, high-current pulse generators designed to drive laser diodes. Applications include biomedical sensors, fiber-optic systems, and LIDAR measurements. Several new products incorporating LASS technology are under development and are planned for release in the coming year.

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